to the instant Office Action as if claims 1, 2 and 4-20 are pending and claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claims 1, 3, and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 11 has been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that claim 11 is vague in definition of the term "active site". Applicants have canceled claim 11 therefore withdrawal of this rejection is respectfully requested.

Claims 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while

being enabling for antisense inhibition of ACAT expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of ACAT; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans. f studies presented in the instant specification. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the references cited do the authors state

or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Braasch and Corey (2002) describes the advances that have been made in the design of antisense compounds over the years. Included in the discussion are the types of advances that are taught in the specification as filed. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*. In fact, the paper states in the abstract that success in clinical trials with these agents has occurred.

The paper by Tamm et al. (2001) is another more recent review of the antisense technology and its specific application to oncology. Again, although the use of antisense is discussed in terms of what can go wrong, the paper again describes advances such as those taught in the instant specification. Nowhere in the reference do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

The paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the

paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The papers by Gewirtz et al. (1996) and Agrawal (1996) are older papers which discuss in general terms issues that were related to older antisense technology. However, nowhere do these papers state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

However, Applicants have amended claim 15 and canceled claims 16-20 in an earnest effort to advance the prosecution and facilitate the allowance of this case. Applicants reserve the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 2, 4 and 5 have been rejected under 35 U.S.C. 102(b) as being anticipated by Chang et al. (US Patent 5,968,749) or Chang et al. (US Patent 5,484,727). The Examiner suggests that these patents disclose the sequence of human ACAT and use of antisense compounds which may be comprised of phosphorothioate linkages to target and inhibit expression of ACAT. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended claim 1, and by dependency claims 2-15, to refer to antisense compounds targeted to specific regions of a ACAT nucleic acid molecule specified by SEQ ID NO. Support for these amendments can be found throughout the specification as filed but in particular at pages 88-91.

Both patents by Change et al. (US Patents 5,968,749 and 5,484,727) disclose the general idea of using antisense as a tool to inhibit expression of ACAT. However, no actual sequences of any particular antisense compounds are taught or suggested by these patents, nor are any examples of successful inhibition of expression using antisense such as are provided in the instant specification. Further, nowhere do these patents teach or suggest antisense compounds from 15 to 50 nucleobases in length that target specific regions of the ACAT nucleic acid molecules of the SEQ ID NO's as now recited in the instant claims. In order to anticipate a claim, the reference cited must teach each and every limitation of the claims (MPEP 2131). Accordingly, these patents fail to teach the limitations of the claims and cannot anticipate the instant invention. Withdrawal of this rejection is respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-14 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (US Patent 5,968,749) or Chang et al. (US Patent 5,484,727), in view of Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to make antisense oligonucleotides to inhibit ACAT because the sequence and antisense inhibition of said protein had been taught by the patents of Chang et al., while the modifications of said antisense are taught by Baracchini et al. The Examiner suggests one of skill would have been motivated to create such compounds due to the teaching of Chang et al. (both patents) where the role of ACAT in producing atherosclerotic plaques is taught. The Examiner suggests one of skill would have had an expectation of success based on the teachings of the Chang et al. patents. Applicants respectfully traverse this rejection.

At the outset, claim 1 and its dependent claims have been amended as discussed *supra* to recite antisense compounds targeted to specific regions of a nucleic acid molecules encoding ACAT of specific SEQ ID NO's.

As discussed *supra*, the Chang et al. patents disclose only the general idea of using antisense compounds to inhibit expression of ACAT, without showing the actual inhibition of expression using antisense. Further, nowhere does this reference teach or suggest antisense compounds targeted to ACAT nucleic acid molecules as claimed, including specific regions of ACAT of SEQ ID NO's 3 or 10. Therefore, this primary references fail to teach the limitations of the claims.

The secondary reference cited fails to overcome the deficiencies in teaching of the primary references.

Baracchini et al. (US Patent 5,801,154) teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere does this patent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to ACAT nucleic acid molecules, or any region of a ACAT nucleic acid molecule.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly,

the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to specific regions of nucleic acid molecules encoding ACAT, cited by SEQ ID NO., and thus cannot render the instant claimed invention obvious. A mere teaching of the concept of using antisense is not sufficient to provide one of skill with the expectation that antisense compounds targeted to specific regions of specific nucleic acid molecules would inhibit expression as claimed. It is with the specification in hand that one of skill would have the information about targeting antisense to regions of ACAT and be shown successful inhibition using specific antisense compounds. Accordingly, withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited. Attached hereto is a marked-up version of the changes made to the specification and claims by the

current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 11 and 16-20 have been canceled without prejudice.

The claims have been amended as follows:

1. (twice amended) A compound 8 to 50 nucleobases in length targeted to a start codon region, a coding region, or a stop codon region of a nucleic acid molecule encoding acyl coenzyme A cholesterol acyltransferase-1 ~~(~~ of SEQ ID NO: 3~~)~~, or a 5'-untranslated region, a start codon region, a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding acyl coenzyme A cholesterol acyltransferase-1 of SEQ ID NO: 10, wherein said compound specifically hybridizes with one of said regions and inhibits the expression of acyl coenzyme A cholesterol acyltransferase-1.

15. (amended) A method of inhibiting the expression of acyl coenzyme A cholesterol acyltransferase-1 in cells or tissues comprising contacting said cells or tissues *in vitro* with the compound of claim 1 so that expression of acyl coenzyme A cholesterol acyltransferase-1 is inhibited.